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We propose a new method to measure the myocardial FDG uptake during fasting and glucose loading in one day, a myocardial FDG-PET one-day protocol, with both 2- and 3-dimensional data acquisition (2D and 3D) without background activity subtraction. To confirm it, we evaluated the effect of scatter correction in the 2D and 3D modes of a PET scanner both in phantom and patient studies. In the phantom study, we used a cardiac phantom with six divided chambers and two cylindrical phantoms placed as the activity outside the field of view. Each chamber was filled with a different concentration of F-18 solution. Regions of interest (ROI) were placed on a polar map generated from reconstructed images and were compared to the concentration of the solution in each chamber in both 2D and 3D. In the patient study, 10 non-diabetic patients with coronary artery disease were studied. Each patient received a myocardial FDG study during fasting (F) and glucose loading (L). L images with background subtraction (Lsub(+)) and without background subtraction (Lsub(-)) were compared by polar map analysis. The ROI counts for the true activity in 2D and 3D demonstrated a linear relationship, and quite similar slopes were observed (0.72 in 2D, 0.69 in 3D). The background fraction in Lsub(-) was $3.59 \pm 1.83\%$. There were significant differences between Lsub(-) or Lsub(+) and F in both normal and ischemic myocardium. Scatter correction was successfully performed in both 2D and 3D modes. Background activity is thought to be negligible and this proposed method is simple to use in measuring the myocardial FDG uptake in one day.

Key words: FDG-PET, fasting, glucose loading, 3-dimensional data acquisition

INTRODUCTION

MYOCARDIAL FDG-PET examination is widely reported to be useful for the detection of ischemia in the fasting state and the assessment of myocardial viability in the glucose loading state; these reports are reviewed by Gropler et al.¹ Although it is thought to be favorable to perform these two examinations on the same day, they are usually performed in separate days. The main reason for this is the longer physical half-life of FDG. If equivalent doses of FDG in both examinations are injected, the second examination

(usually the glucose loading exam) will be affected by the tracer injected for the first examination. An extremely small amount of FDG injected in the first examination to eliminate the effect of the first-injected tracer may diminish the quality of the fasting image.

The measurements of myocardial FDG uptake during fasting and glucose loading could be performed in one day if a 3 dimensional acquisition with a small amount of FDG were used for the fasting study and a subsequent 2 dimensional acquisition with a large amount of FOG for the glucose loading study (myocardial FDG-PET one-day protocol), because the 3D acquisition has a much higher counting sensitivity than conventional 2D acquisition. A whole-body PET scanner, ADVANCE, developed by General Electric (GE-YMS, Tokyo, Japan), enabled 3D data acquisition with retracted septa. Its performance was previously described² with cylindrical

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phantoms, but the performance of 3D acquisition for cardiac PET imaging has not been well validated. In particular, scatter from the radioactivity outside the field of the view may be an issue in 3D acquisition.

The purpose of this study was to assess the feasibility of myocardial FDG PET one-day protocol in patients with coronary artery disease by using a combination of 3D and 2D acquisition. Prior to the clinical study, we performed a phantom study to assess the accuracy of 3D acquisition PET for radioactivity quantification.

MATERIALS AND METHODS

Phantom Study

Phantom preparation

In the phantom study three phantoms, one cardiac (RH-2, Kyoto Kagaku, Co., Ltd. Kyoto, Japan) and two cylindrical, were used. The cylindrical phantoms were placed in the upper and lower positions of the cardiac phantom, to simulate the radioactivity in the head and neck (upper position), and liver and urine in the bladder (lower position) as the radioactive material outside the FOV in the human body. The myocardial chamber was divided into six segments, and each segment was filled with 55, 45, 35, 29, 24, or 12 kBq/ml of F-18 solution. The left ventricle and mediastinal chamber were filled with 8 kBq/ml of F-18, the head and neck with 8 kBq/ml, and the liver and urine with 12 kBq/ml. These radioactivities except in the myocardial chamber were decided based on the clinical data we examined.

PET imaging

The ADVANCE whole-body PET scanner was used for imaging. The physical characteristics of this scanner were previously described in detail.³ The spatial resolution of the reconstructed PET images is 8 mm in FWHM at the center of the field of view and axial resolution is 4 mm in 2D and 10 mm in 3D. Data acquisition was performed for 20 min in 2D. Just after 2D scanning, 3D data acquisition was performed for 20 min. One day after the emission scan, a 10-min transmission scan was performed with two rotating Ge-68 pin sources for attenuation correction. During the entire phantom study, the phantom was placed in the same position so that misregistration between the emission and transmission scan did not occur.

Image preparation and data analysis

All data acquired in the phantom study were reconstructed with scatter correction by the filtered back-projection method. The reconstruction filter was a Hanning 6 mm and Ramp in 2D and 3D. For filtering in the Z-axis direction in 3D, a Hanning filter (cut off; 8.5 mm) was applied. From reconstructed transaxial images, short axis (SA), vertical long axis (VLA) and horizontal long axis (HLA) images were generated. Then a polar map was generated with SA images in 2D and 3D. Circular regions

of interest (ROIs), 10 pixels (30 mm) diameter in size, were placed on each myocardial chamber shown in Figure 1, and the value for each ROI was compared to the concentration of the F-18 solution in each chamber, so that the decay of the counts was corrected to the mid-time of each scan. The ratio of the ROI's value to the FDG concentration in 2D and 3D images was compared, and the ROI values in 2D and 3D were compared.

Patient Study

Subjects

We examined 10 subjects, 7 males and 3 females. Their ages ranged from 63 to 77 years (69.4 ± 5.5 yrs). All subjects had coronary artery disease (6 single-, 3 double-, and 1 triple-vessel disease) and a history of old myocardial infarction. Patients with diabetes mellitus (DM) were excluded from this study as diabetes deteriorates image quality in the glucose loading state.^{4,5} The values for serum glucose in the fasting state were applied for the exclusion of DM patients.

PET imaging

The same PET scanner as used in the phantom study was applied for the patient study. Each patient's body was fixed with a Velcro band and positioned carefully with a light beam. After overnight fasting and transmission scan for 10 min, 3D FDG data in fasting were acquired with 60 min postinjection of 60.1 ± 22.8 MBq of FDG for 10 min. One hour after the first scan, patients received oral glucose loading (75 g glucose/225 ml). The loading amount was decided in proportion to the patient's weight (1.25 g/kg, 75 g maximum). After glucose loading, the patient lay on the scanner bed and underwent data acquisition as the background activity (BKG) in fasting in 2D. One hour after glucose loading, 365.9 ± 20.9 MBq of FDG was injected, and 1 h later 2D FDG data on glucose loading were acquired. In each study, pre- and post-injection

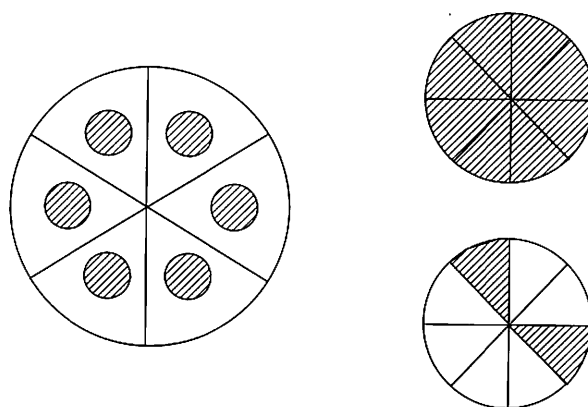


Fig. 1 The template of regions of interest (ROIs) in phantom study (left), global ROI method (right upper), and regional ROI method (right lower) in clinical study. In regional ROI method, each fan-shape area is defined as regional ROI.

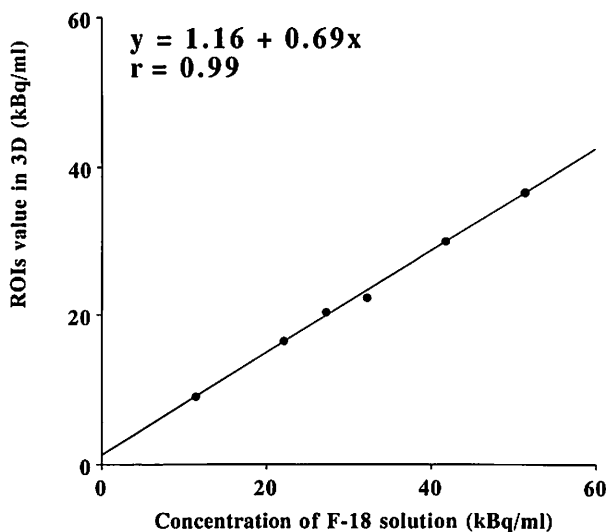
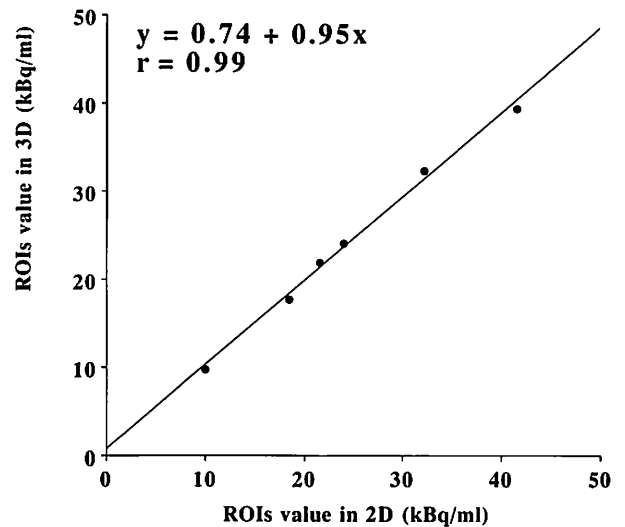
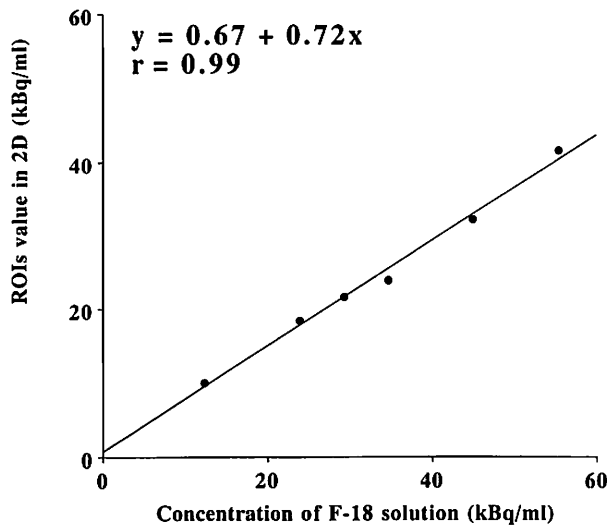


Fig. 2 The effect of scatter correction in 2D (a) and 3D (b). In every concentration of F-18 solution, ROIs value correlated linearly and quite similar slopes between 2D and 3D were demonstrated. The relationship of ROIs value between 2D and 3D was almost unity (c).

from SA images for quantitative analysis. Finally, the following polar map images were prepared for data analysis: 3D fasting FDG images (F) and 2D glucose loading FDG images with background subtraction (Lsub(+)) and without background subtraction (Lsub(-)). Each polar map was divided into 8 segments, shown in Figure 1 (right lower), for the regional ROI analysis described later.

Data analysis

To assess the necessity of background correction, two methods were used. One, a large circle ROI (Fig. 1, right upper) which covers the whole region of the polar map was placed (global ROI method), and the background fraction in Lsub(+) in each patient was calculated with the following equation:

$$\text{Background fraction (\%)} = \frac{\text{Lsub(-)} - \text{Lsub(+)}}{\text{Lsub(+)}} \times 100$$

In the other method, the segments were divided into two groups (regional ROI method), high SUV (FDG-high) and low SUV (FDG-low) group in F, and a background fraction in both groups was calculated with the equation shown above. The FDG-high area was defined as an area where increased FDG uptake was observed in a 3D fasting image and this area was also defined as an ischemic area. We also compared the difference between SUV in Lsub(-) or Lsub(+) and F to assess whether the background subtraction will affect the difference in SUV between F and L or not. Tamaki et al.⁶ reported that the FDG uptake index linearly correlates with the metabolic rate of glucose (MRGlu) in both fasting and postprandial

doses were measured to calculate the standardized uptake value (SUV) of FDG in the myocardium. Serum glucose, insulin and free fatty acid (FFA) levels were measured at the point of FDG injection before and after glucose loading to observe the changes in them during glucose loading.

Image preparation and Data analysis

Image preparation

The parameters for the image reconstruction were the same as those used in the phantom study. A BKG image was subtracted from the glucose loading FDG image to generate a BKG subtracted loading image. The unit of reconstructed transaxial FDG images was converted from tissue activity (unit: kBq/ml) to SUV (unit: mg/ml) with the injected dose of FDG and body weight in each patient. From all SUV images in FDG, SA, VLA and HLA images were generated. Thereafter a polar map was generated

Table 1 The change of biochemical data before and after glucose loading

	Fasting	Glucose loading	p value
Glucose (mg/dl)	102 ± 12	200 ± 17	< 0.0001
FFA (mEq/l)	0.59 ± 0.25	0.28 ± 0.16	0.0011
IRI (μU/ml)	10.3 ± 6.5	46.6 ± 25.1	0.0019

serum glucose level (unit; mg²/(ml*dl)). With this index, we compared the difference in the corrected SUV for Lsub(-) of Lsub(+) and F.

Statistical analysis

All data are shown as the mean ± SD. The difference between the two groups in the mean values was analyzed by a nonparametric test (Mann-Whitney U test). p < 0.05 defining what is significant.

RESULTS

Phantom Study

Each ROI value for the concentration was linearly correlated ($y = 0.72x + 0.67$, $r = 0.99$ in 2D; $y = 0.69x + 1.16$, $r = 0.99$ in 3D; x means the concentration of F-18 solution and y means the ROI value in each chamber, Fig. 2a, 2b). ROI values in 2D and 3D also had an excellent linear relationship although slight underestimation in 3D was observed (Fig. 2c). The ratio of the ROI value to the concentration for 2D and 3D showed no significant difference ($p = 0.44$).

Patient Study

Table 1 shows the difference between the levels of serum glucose, insulin, and FFA before and after glucose loading. After glucose loading, serum glucose and insulin levels rose significantly, and the FFA level fell, which indicates the physiological change after glucose loading.

The background fraction was $3.59 \pm 1.83\%$ with the global ROI method, $5.22 \pm 2.35\%$ in FDG-high, and $2.37 \pm 2.27\%$ in FDG-low with the regional ROI method.

Figures 3a and 3b shows the differences between normal and ischemic areas in F and L images. A significant difference between F and Lsub(-) was observed ($p < 0.001$) in both normal and ischemic myocardium. F and Lsub(+) also showed a significant difference ($p < 0.001$).

DISCUSSION

Myocardial FDG-PET studies have been performed in many laboratories and hospitals, and are reported to be useful for the assessment of myocardial viability in the fasting and/or glucose loading states.¹ But several disadvantages were also reported in the fasting (heterogeneity of myocardial FDG uptake,^{7,8} overestimation of ischemic myocardium⁹ and glucose loading states (underestimation of myocardial viability).^{9,10} Therefore, it is advantageous to perform both examinations on the same patient to supplement each disadvantage, and the subtraction data from the glucose loading state to the fasting state might provide additional information about myocardial viability. Indeed, such an attempt has been made previously.¹¹ But Niwayama et al. reported¹¹ that the major problem with this method was that these two examinations must be done on separate days. The reason for this is the longer

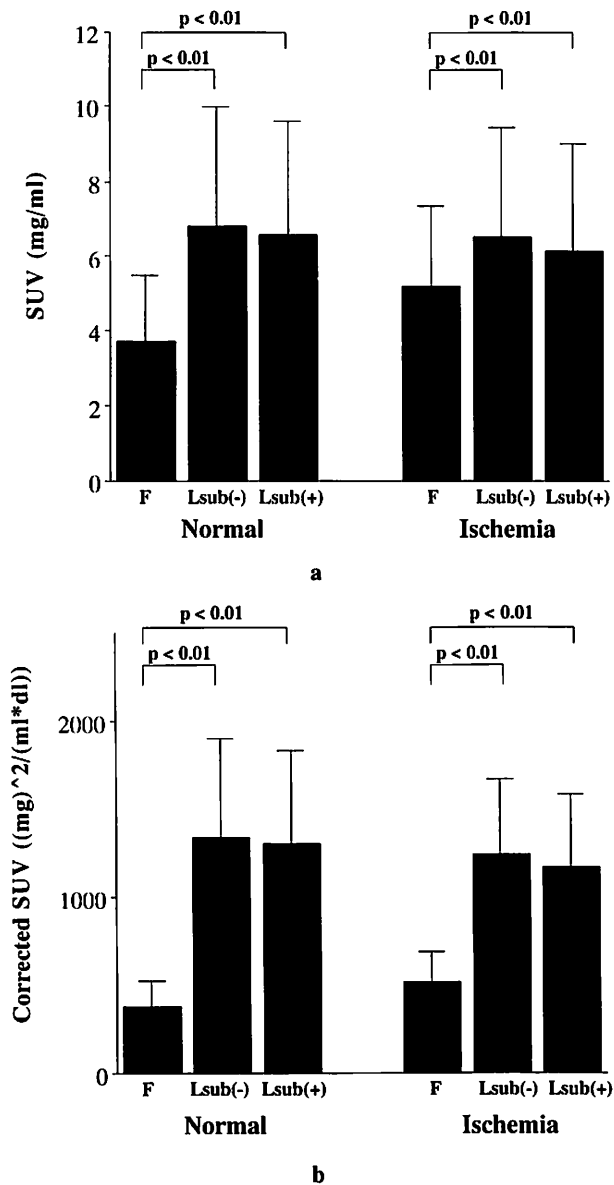


Fig. 3 Differences of SUV (a) and corrected SUV (b) between Lsub(-) or Lsub(+) and F in normal and ischemic area. Background subtraction does not affect the result of statistical analysis between L and F.

conditions although underestimation of the FDG uptake index is seen in the postprandial state. Therefore, we used another index which takes account of the serum glucose level, corrected SUV, which is the product of SUV and the

physical half life of FDG which is mentioned in the introduction to the current study.

We tried to solve this problem by using a PET scanner that can acquire both 2D and 3D data. In the 3D mode, the septa was retracted and the acceptable angle was set to ± 11 to obtain flat sensitivity from 11 to 24 slices, and approximately six times higher counts can be obtained than with 2D. In addition, a higher noise-equivalent count ratio (NECR) can be obtained in the low radioactivity range (less than 37 kBq/ml).³

We had to confirm the effect of scatter correction in 3D when the radioactive material was placed outside the FOV because we were going to assess the FDG uptake in 2D and 3D images quantitatively. Although the effect of scatter correction in 3D with and/or without radioactive material outside the FOV in a cylindrical phantom was previously reported,² we thought it would be better to evaluate it under more appropriate conditions. Our results indicated that scatter correction in 3D was performed well and that SUVs in 2D and 3D are available for comparison. The reason why the slope of ROI value against the concentration had become far from unity is thought to be due to the partial volume effect. The cross-calibration factor is calculated with a cylindrical phantom which can neglect the partial volume effect. In contrast, the cardiac phantom used in this phantom study has only a 10 mm myocardial chamber thickness and this might have caused underestimation.

To assess the necessity of background subtraction, the background fraction in the global ROI method is 3.59% on average, and this value was thought to be enough to negate the effect of background activity. In the regional ROI method, although the background fraction in FDG-high areas showed a relatively higher background fraction, this did not affect the result of the comparison of F and L images in either normal or ischemic myocardium. These data for fasting and glucose loading images were therefore thought to be independent without background subtraction.

In this study we first applied SUV for quantitative analysis. Tamaki et al. reported⁶ that the FDG uptake index which is a semi-quantitative value like SUV demonstrated an excellent linear relationship with the regional metabolic rate of glucose (MRGlu) in the fasting condition although underestimation of the FDG uptake index compared with MRGlu was also observed in the glucose loading state. This means that the difference between fasting and glucose loading with the semi-quantitative value will be smaller than that with the absolute value. We therefore proposed a corrected SUV, which takes account of serum glucose levels. With this index, the dynamic range of the quantitative value for fasting and glucose loading improved as demonstrated in the measurement of MRGlu. The limitation with this index is that it does not take into account change in the lumped constant (LC). Bøtker et al.¹² reported that the LC varies in the hyper-

insulinemic state and MGU will be underestimated if the conventional value for LC is used. But in a clinical situation, it is impossible to measure LC even in the measurement of MRGlu, so that corrected SUV was thought to be simpler and a clinically suitable index for quantitative assessment.

In patient studies, the serum glucose level after glucose loading rose higher than expected in normal subjects. According to the diagnostic criteria of DM in a 75 g oral glucose tolerance test, less than 160 mg/dl 1 h after loading is normal. This indicates that patients with DM or impaired glucose tolerance may be included in our study and the fasting serum glucose levels alone is inadequate for the exclusion of DM subjects. To exclude such patients, strict criteria will be required.

The results indicate that the measurement of fasting and glucose loading myocardial FDG uptake in one day seem to be feasible with a combination of 2D and 3D data acquisition. Considering the increasing number of PET scanners which are capable of 3D acquisition, our imaging protocol may eliminate the need for visiting PET laboratories twice on separate days, and thus may be beneficial for patients.

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